Armed Forces College of Medicine

AFCM

Neuroscience Module

Lecture (7)

Neurological disorders related to amino acids metabolism (1)

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Key points

The biochemical basis of maple syrup urine, homocystinuria and pellagra

INTENDED LEARNING OBJECTIVES (ILO)

By the end of this lecture the student will be able to:

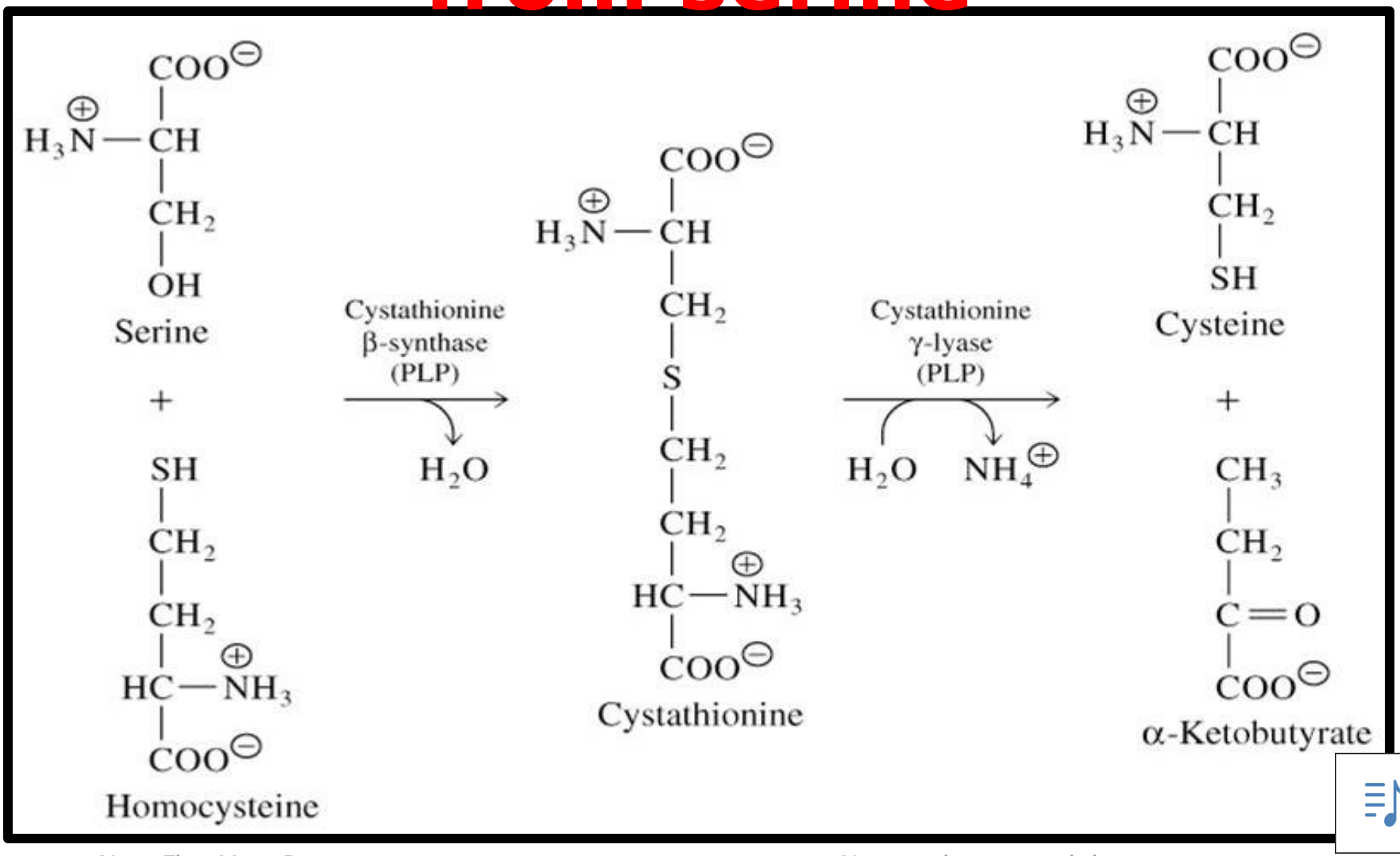
1. Identify the metabolic defects in maple syrup urine, homocystinuria and pellagra

The metabolic disorders related to defects in amino acids metabolism

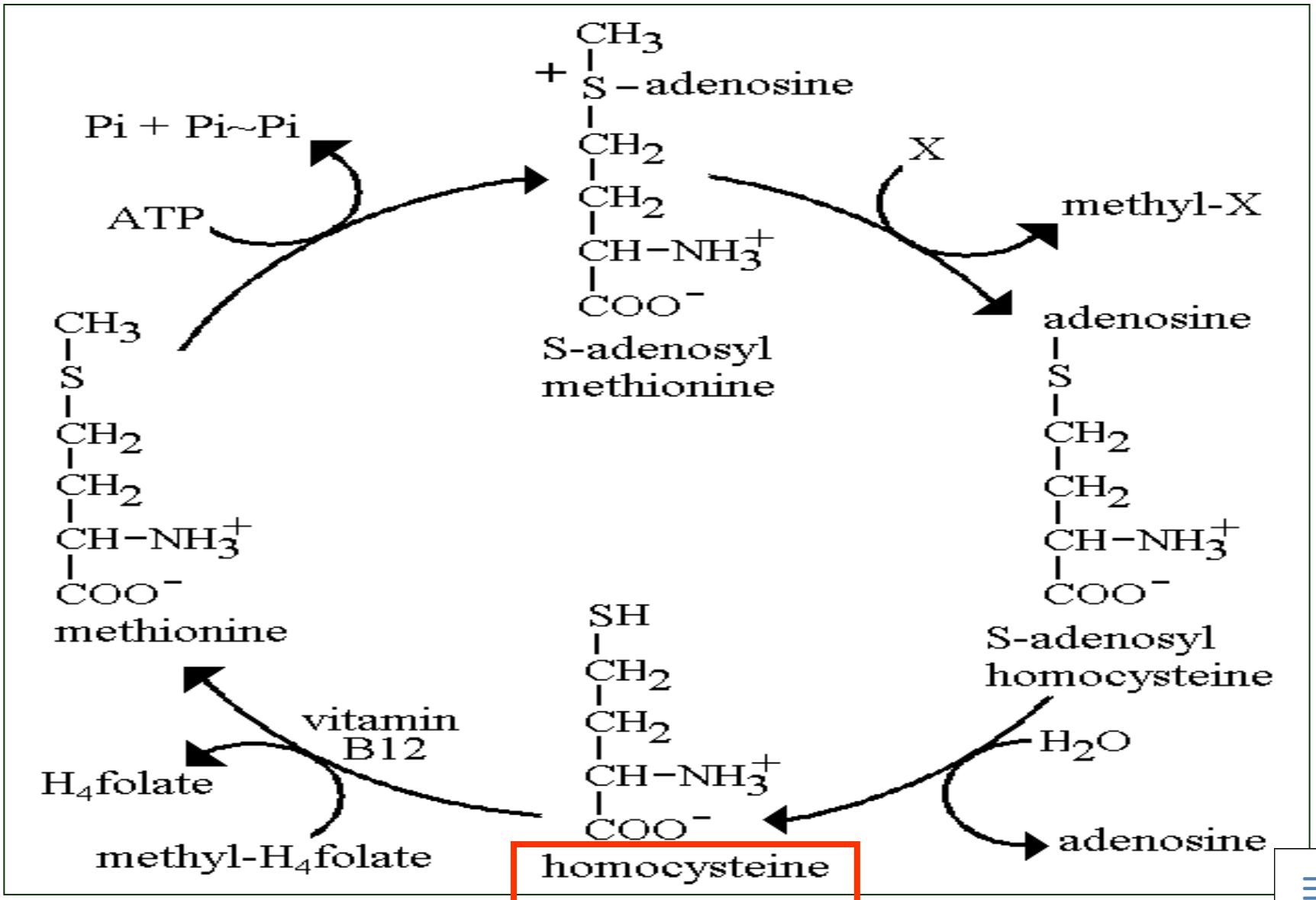
- **Glycine:** glycinuria, and primary hyperoxaluria (refer to metabolic pathways of the kidney).
- **Cysteine:** Cystinuria, Cystinosis (refer to metabolic pathways of the kidney) and Homocystinuria.
- **Branched chain amino acids:** maple syrup urine disease.
- **Tryptophan:** hartnup disease (refer to metabolic pathways of the kidney) and pellagra.
- **Phenylalanine and tyrosine:** albinism, phenylketonuria and alkaptonuria.

Metabolism of homocysteine

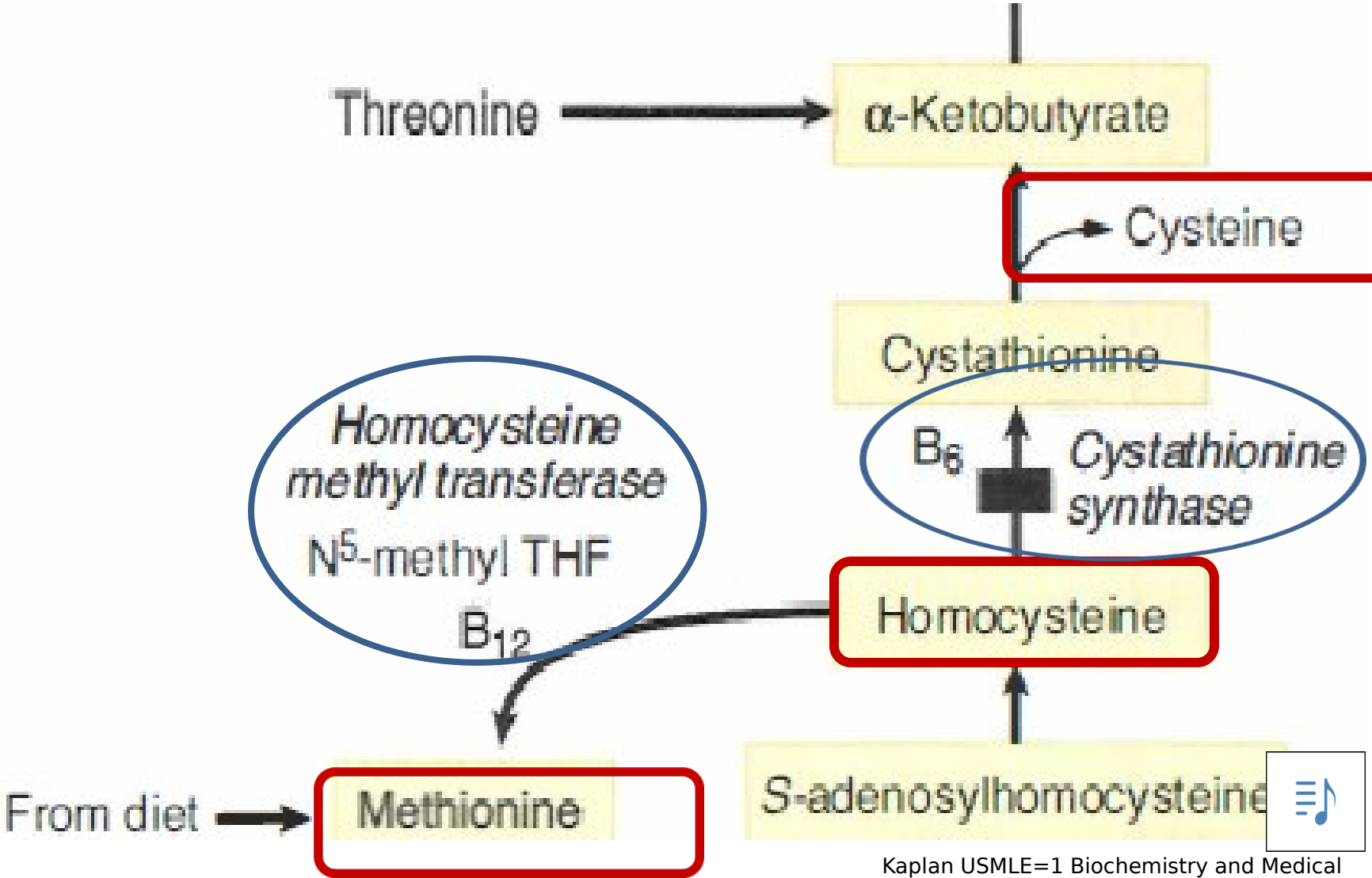
1) Biosynthesis of cysteine from serine



Metabolism of homocysteine



Metabolism of homocysteine



(1) Homocystinuria

1) due to defect in cysteine synthesis due to:

A-Deficiency of cystathionine synthase or cystathionine lyase

B-Deficiency of PLP

2) Defect in conversion of homocysteine to methionine due to deficiency of:

A- Folic acid

B- Vitamin B12

C- Homocysteine methyl transferase

Clinical picture

1) **Coronary heart disease: due to atherogenic effect of homocysteine.**
2) **Weak extracellular matrix: homocysteine binds to lysine of collagen and prevents cross linking.**

Manifested by:

a) **mental retardation**
b) **Bone deformities**
c) **Dislocation of the lens.**

3) **Thrombosis: the major cause of early death in these individuals.**

Treatment

A) Defect in cysteine synthesis:

1) Supplementation of cysteine
2) pyridoxine (vitamin B6), which is converted to pyridoxal phosphate

B) Defect in regeneration of methionine:

3) Decrease methionine in diet
4) Supplementation of folic acid or vitamin B12
5) Supplementation of choline as methyl donor

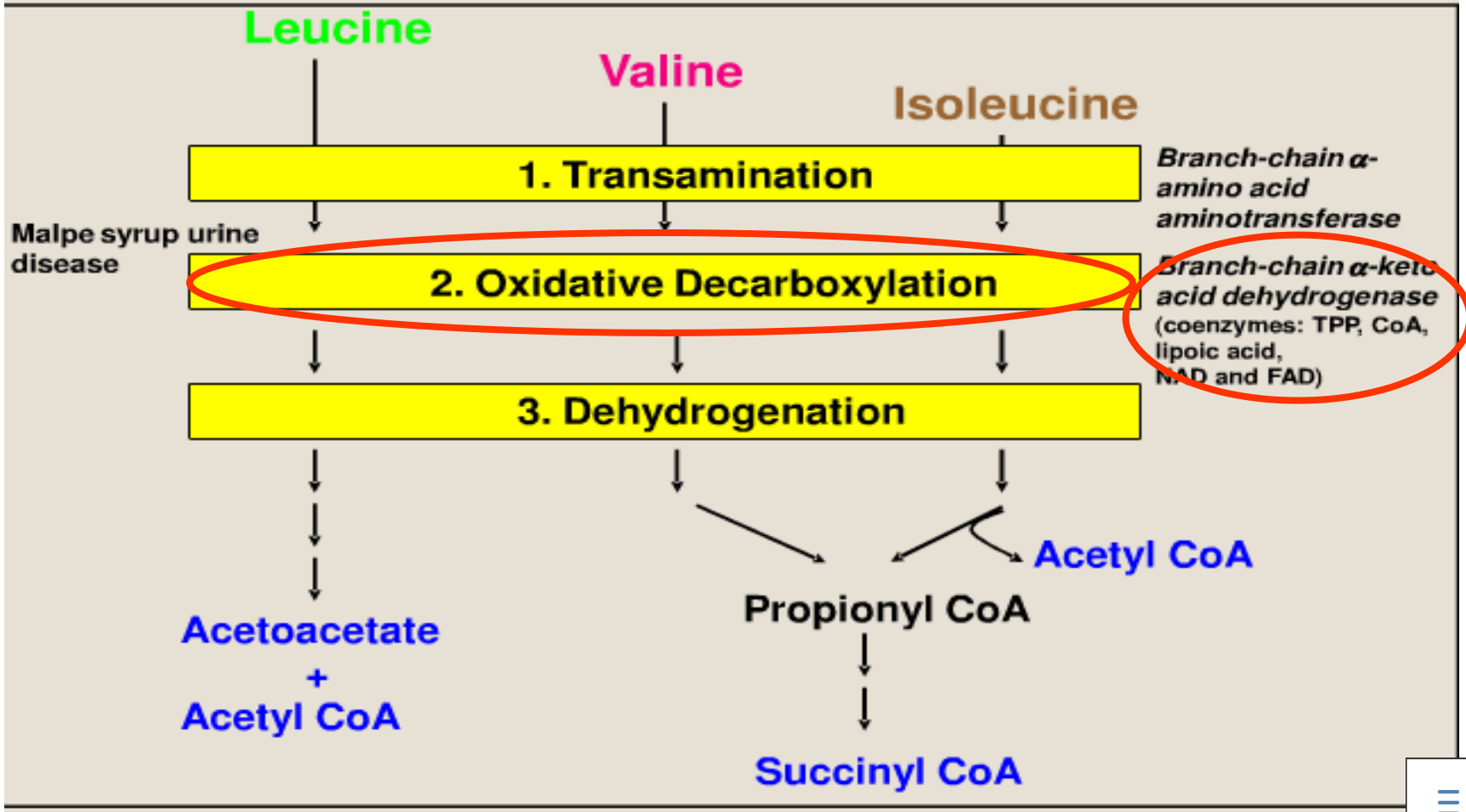
The biochemical basis of maple syrup urine, homocystinuria and pellagra (Quiz)

Explain the biochemical basis of homocystinuria

Case study

A 10-day-old male infant had recurrent generalized convulsions. The odor of burned sugar from the body and urine was also noted. Plasma and urine amino acid analysis disclosed a marked increase in the concentration of branched chain amino acids (BCAA). He was diagnosed as maple syrup urine disease (MSUD)

Branched-chain Amino Acids Catabolism



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(2) Maple Syrup Urine Disease

- **It results from deficiency of the dehydrogenase complex which catalyzes the oxidative decarboxylation step.**
- **The branched chain α-AAs and their corresponding α-keto acids accumulate in blood causing a toxic effect that interferes with brain functions.**
- **The disease is characterized by mental retardation and may lead to early death.**
- **The urine has a sweet smell-like maple syrup or burned sugar due to rise in isoleucine.**
- **TTT: diet low in branched α-AAs**

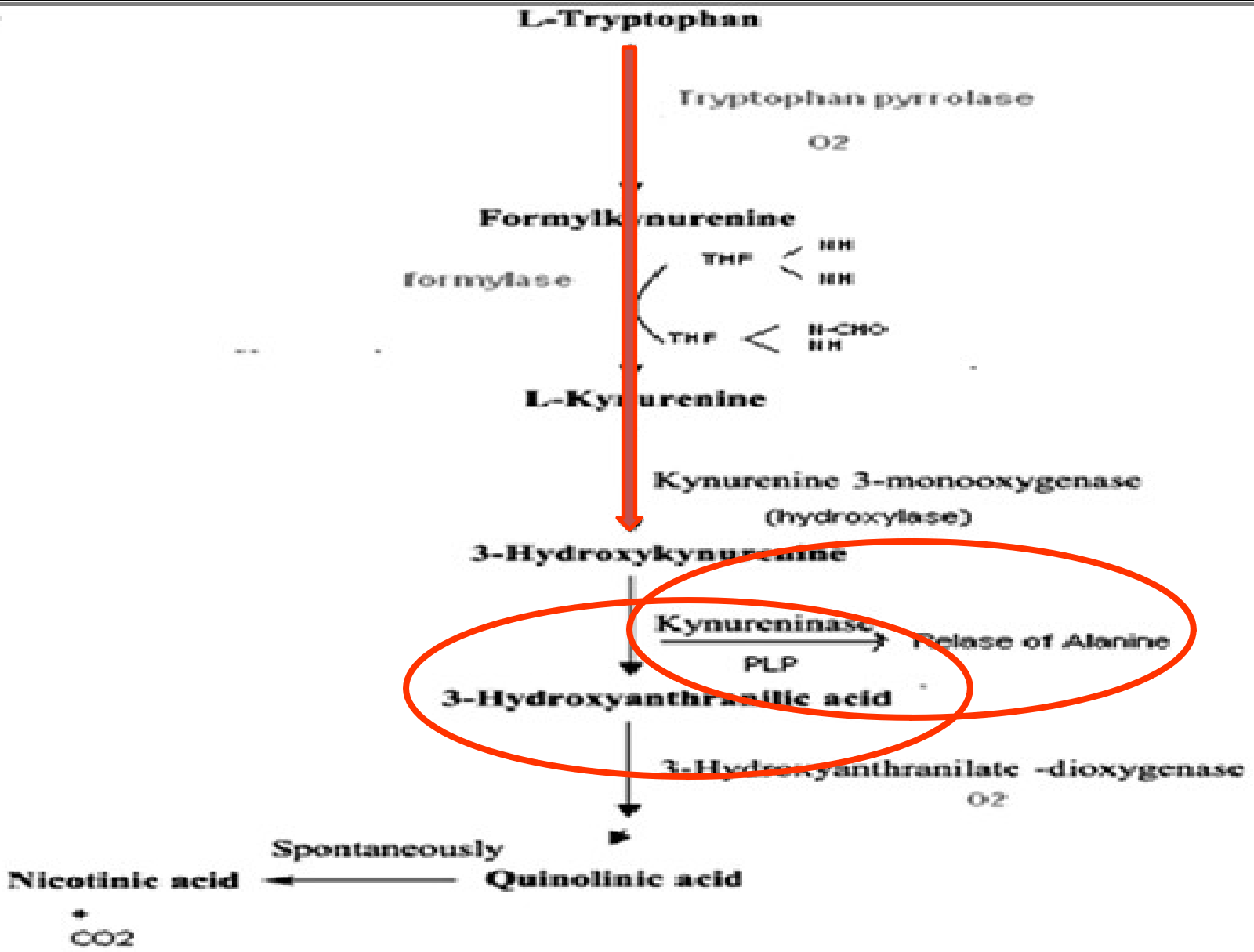
The biochemical basis of maple syrup urine, homocystinuria and pellagra (Quiz)

Explain the biochemical basis of maple syrup urine disease

Metabolic disorder of Tryptophan metabolism:
Pellagra

Pellagra is a disease that results from nicotinic acid deficiency

Biosynthesis of nicotinic acid (NIACIN)



Causes of pellagra

1- Decrease tryptophan in diet.
2- Decrease tryptophan absorption (Hartnup disease).
3- Pyridoxal-phosphate deficiency.
4- Carcinoid tumour (60% of tryptophan is converted into serotonin → ↓ production of nicotinic acid.

Manifestations of pellagra (3 D)

A.Dermatitis:rough skin dark skin on the exposed parts of the body

B.Diarrhea

C.Dementia

https://www.google.com/search?q=pellagra&hl=en-US&source=lnms&tbm=isch&sa=X&ved=0ahUKEwiDosalro7kAhVEyhoKHQBMAaYQ_AUIESgB&biw=1366&bih=613

Treatment of pellagra

1- Treatment of the cause.
2- Nicotinic acid supplement.

Lecture Quiz

USMLE Question

A 63-year-old man who is an alcoholic is brought into the emergency department by his daughter. She states that the patient's memory has been very poor, and he constantly creates elaborate yet untrue stories. Physical examination reveals ataxia and bilateral horizontal nystagmus. Wernicke-Korsakoff syndrome, caused by a water-soluble vitamin deficiency, is suspected. Which of the following conditions is also a result of a water-soluble vitamin deficiency?

(A) Increased erythrocyte hemolysis
(B) Neonatal hemorrhage
(C) Night blindness
(D) Osteomalacia
(E) Pellagra

Summary

- Homocystinuria is a disorder of methionine metabolism, leading to an abnormal accumulation of homocysteine and its metabolites in blood and urine causing serious problems.
- Maple syrup urine disease (MSUD) is a metabolic disorder affecting branched-chain amino acids. The condition gets its name from the distinctive sweet odor of affected infants' urine.
- Pellagra is a disease caused by a lack of the vitamin niacin (vitamin B3). Symptoms include inflamed skin, diarrhea, dementia, and sores in the mouth. Areas of the skin exposed to either sunlight or friction are typically affected first.

SUGGESTED TEXTBOOKS

- Lippincott's illustrated reviews in Biochemistry by P.C. Champe, R.A. Harvey and D.R. Ferrier
- Fundamentals of Clinical Chemistry (Tietz)
- "Textbook of Biochemistry with Clinical Correlations" by T.M. Devlin
- "Harper's Biochemistry" by R.K. Murray, D.K. Granner, P.A. Mayes and V.W. Rodwell

THANK YOU